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L13: Entry 1 of 2

File: USPT

Aug 20, 1996

DOCUMENT-IDENTIFIER: US 5547576 A

TITLE: Pathogenic substance removing material and a blood filter containing the material

Abstract Text (1):

A material wherein a polyamine compound is immobilized on its base surface and a blood filter using this material. The material is provided in the form of a porous membrane having the maximum pore diameter of 0.1-50 μm . The polyamine compound is at least one compound selected from the group consisting of (a) a polyamine compound which has primary and secondary amines in its molecule and a hydrophobic part between these amines, (b) a polyamine compound represented by the following formula (I); ##STR1## wherein R.sup.1, R.sup.2, R.sup.3, R.sup.4 and R.sup.5 represent hydrogen, aliphatic and aromatic hydrocarbons, and halogen, and n is 5 or more, and (c) a polyamine compound represented by the following formula (II); ##STR2## wherein R represents NH.sub.2 or aminoalkyl radical having 1 to 4 carbon atoms and n is 5 or more. The blood filter comprises a housing which has an inlet and outlet, and the material arranged inside the housing.

Brief Summary Text (3):

The present invention related to a material which can selectively remove pathogenic substances containing leukocytes, platelets and virus from a protein containing solution.

Brief Summary Text (5):

Currently in the field of medical care, the need to more drastically and selectively remove virus, leukocytes, platelets, etc. from the body fluid such as blood and plasma is increasing all the more. For example, it is an accepted criterion that the blood for transfusion should not contain virus, and that, as a rule, component transfusion should give only the blood component required for the patient and no unnecessary components. However, despite the fact that it is called component transfusion, the concentrated erythrocyte preparations in general use actually contain a large quantity of leukocytes and platelets. When such concentrated erythrocyte preparations are transfused to the patients who should frequently receive transfusion (those with aplastic anemia, hemolytic anemia, chronic hemorrhagic anemia, etc.), antibody against to leukocytes and platelets is produced, and there is also a possibility of transfusion reactions. To inhibit the generation of antibody to leukocytes and platelets and to prevent transfusion reactions, it is necessary to provide erythrocyte preparations of high purity by removing leukocytes and platelets therefrom. Recently Graft-versus-Host Disease (GVHD) is posing a problem. In this disease, the lymphocytes with division potential which are present in the transfused blood acknowledge the histocompatibility antibody of the patient as the foreign matter and attack it. For this reason as well, the demand for the blood preparations from which leukocytes are removed is on the increase. To this end, it is necessary to remove lymphocytes from the blood for transfusion by a blood filter or to destroy the division potential of lymphocytes by radiation.

Brief Summary Text (9):

As a method which impart the function to selectively recognize cell, virus or biologically derived substance to the membrane surface, there is a method to take advantage of the selective recognition function of a living body, for example, antigen-antibody, enzyme-substrate and receptor on the cell surface. However, this is an expensive method since the substance used as a ligand should be biologically derived protein and is therefore vulnerable to heat and acid, making it difficult to sterilize and handle.

Brief Summary Text (10):

Zierdt and others reported that they found particles such as bacteria, erythrocytes, leukocytes, platelets and polystyrene beads could still be captured when a fluid containing the particles were filtered through a membrane having a larger pore size than the particle size (Applied and Environmental Microbiology, 1979, 12, 1166-1172). They concluded that the capture was attributable to a electrostatic interaction since particles were not captured by the membrane treated with anion surfactant, and indicated that it would be possible to adhere and capture leukocytes and platelets through electrostatic interaction by means of surface electric charge.

Brief Summary Text (11):

In this regard, there is a description in U.S. Pat. Nos. 3,242,073 and 3,352,424 on the removal of platelets having negative surface charge from a fluid by using a filter material which is prepared by electrostatically binding cationic organic poly-electrolytes to anionic filter. In Unexamined Published Japanese Patent Application No. 3-207413, a filter material which possesses quarternary ammonium groups on the surface and positive zeta potential at pH 7 is described. However, when the blood is filtered through such cationic filter, the concentration of the factors released from platelets goes up and thus deteriorates the quality of blood preparations after filtration despite the improved capture rate of leukocytes and platelets.

Brief Summary Text (12):

On the other hand, isoelectric point (pI) of many virus particles is 3-6, and thus they have negative charge in the neutral range, adhesion of virus is possible through electrostatic interaction from the water containing less impurities. As the material for removing virus, there are porous membrane and material having polycationic structure on the surface such as polyvinyl pyridinium described in Unexamined Published Japanese Patent Application No. 3-123630. However, it was difficult to selectively remove virus with conventional cationic filter since non-specific adsorption of protein to the cationic surface occurs in a solution with high protein concentration such as plasma and blood.

Brief Summary Text (13):

As a filter to remove virus from body fluid and protein containing solution, regenerated cellulose membrane described in Unexamined Published Japanese Patent Application No. 2-167232. As the pore size of this membrane is smaller than that of virus particle, virus cannot pass through the membrane. However, the transmission speed is low due to the small pore size, and clogging of the membrane often occurs.

Brief Summary Text (14):

As a material to separate virus from blood and plasma by making use of biological affinity, International Patent Publication No. WO 89/01813 describes a material in which the receptor of the virus existing on the cellular surface is fixed to its surface. However, the process of purifying receptor from cell and that of binding the receptor to the base are complicated in this method. Furthermore, the use of biologically derived component creates problems of cost, functional stability and time course change.

Brief Summary Text (15):

Though the membrane technology used for separation is a technology widely used in the industry through researches on ultrafiltration membrane, reverse osmosis membrane, ion exchange membrane, gas separation membrane and osmotic gasified membrane. However, most of them are based on the separation through the difference in concentration, pressure and potential making use of membrane pore, and there are few separation membranes designed by positively introducing selective recognition mechanism into the membrane surface.

Brief Summary Text (17):

The present invention aims at providing a material which can selectively remove pathogenic substances containing leukocytes, platelets and virus from a protein containing solution, and which may constitutes a membrane with excellent processing speed and easy to handle when used as a porous membrane and the like.

Brief Summary Text (24):

The pathogenic substance selectively removing material of the present invention is preferably provided in the form of porous membrane and its maximum pore size is preferably 0.1-50 .mu.m.

Brief Summary Text (25):

It is easy to handle the pathogenic substance selectively removing material of the present invention since polyamine compound is immobilized in the surface of the material, and when this material is provided in the form of a porous membrane, an excellent membrane which allows simple and speedy processing will be obtained.

Brief Summary Text (26):

The pathogenic substance selectively removing material of the present invention is preferably used for removing virus, leukocytes and platelets contained in a protein containing solution such as body fluid including blood and plasma. In addition, it is also useful in the research for cell recognition, separation, and concentration and the construction of culture systems. Furthermore, since it is able to recognize and remove virus in an environment in which protein or the like exist, i.e. plasma, it can be effectively used in the prevention of virus contamination and virus infection in the food industry, fermentation industry, pharmaceutical industry and medical institutions.

Brief Summary Text (28):

The pathogenic substance selectively removing material used for the blood filter of the present invention is preferably in the form of porous membrane, and more preferably having the maximum pore size of 5-50 μm .

Detailed Description Text (2):

Polyamine compound is a compound which every living body possesses whether it is a eucaryotic cell or procaryotic cell. The compound is known to act on various biological polymers including cell membrane and nucleic acid which have abundant negative charge to influence their functions (refer to "Kagaku to Seibutsu" or Chemistry and Biology, vol. 28, No. 3, 162-171, 1991 by Akira Shirahata; The Physiology of Polyamines, ed. by U. Bachtach and Y. M. Helmet, CRC Press, Boca Raron, 1989; The Biochemical Journal, vol. 260, pages 1-10, 1989, F. Schuber).

Detailed Description Text (3):

On the other hand, the polyvalent cationic compound such as polyvinyl pyridinium that has quaternary ammonium structure in the molecule and the compound having hydrophobic radicals demonstrate strong interaction with protein. As a result, non-specific adsorption increases and the cell and virus selectivity is lost in these compounds in the existence of protein as seen in blood and liquid culture medium. Many cells have glycoprotein having negative charge on the cell surface and are known to electrostatically bind to high molecular weight polycations. However, as an interaction is too intense in the high molecular weight polycations such as strongly basic compound having quaternary ammonium salt and the compound having hydrophobic part, the damage to cells and to cell selectivity becomes large. While the polyamine compounds used for the material of the present invention possesses basicity and molecular structure which act easily on cells and virus, its low degree of interaction with the coexisting protein makes it possible that the material selectively capture cells and virus.

Detailed Description Text (4):

Even a simple virus found in a vertebrate has several proteins and polypeptides but very complicated virus, e.g. pox virus, has over 100 kinds of these substances. A simple virus which does not have an envelope is encased in a protein shell called capsid. In the virus which has an envelope, a glycoprotein called peplomer which projects from the envelope exists on the surface of virus particle. For this reason, the virus particle has either positive or negative surface charge. Many viruses have anionic part derived from anionic phospholipid, sialic acid, or capsid protein, and are known to adsorb through electrostatic interaction to high molecular weight polyvalent cations. However, selective adsorption of virus is not possible in an environment such as liquid culture medium and plasma, in which protein coexist, since the electrostatic interaction is too intense in a strongly basic compound having quaternary ammonium salt and high molecular weight polycation which possesses hydrophobic part.

Detailed Description Text (5):

Among polyamine compounds, polyethyleneimine is an optimal material for ligand since it is a water soluble polymer which has many amines in its molecule, and is low price. Since interaction with protein is comparatively weak in polyethyleneimine itself, non-specific adsorption of protein is suppressed and selective adsorption of virus is possible by controlling the amount of its surface presence even when it is immobilized to the surface of the base.

Detailed Description Text (6):

The pathogenic substance selectively removing material of the present invention is a

material which can remove pathogenic substances such as virus, leukocytes and platelets from a protein containing solution. Some of the examples of protein containing solutions are body fluid such as blood, plasma, serum and urine, liquid culture medium of cell and microorganism or a solution containing protein component derived from these fluids. The pathogenic substance selectively removing material of the present invention is a material which can selectively adhere and remove pathogenic substances from a fluid particularly containing plasma and plasma protein.

Detailed Description Text (19):

Immobilization of a polyamine compound to the base surface means that it is bound to reactive functional groups on the surface of the base so that the polyamine compound does elute from the surface. The binding of polyamine compound and reactive functional groups shall preferably be done by covalent bond. The amount of polyamine compound immobilized to the base material may be measured by titration using perchloric acid. When the pathogenic substance selectively removing material is provided in the form of porous membrane, the amount of polyamine compound immobilized to the surface of base material is preferably 1×10^{-4} eq/g or more, or more preferably 4×10^{-4} eq/g or more.

Detailed Description Text (20):

As a method to immobilize polyamine compound to the surface of base material, it is possible to use any methods known in this field. For example, after introducing functional groups such as epoxy groups, amino groups, aldehyde groups, carboxyl groups, hydroxyl groups and acid chloride groups by graft polymerization method, coating method, chemical modification and oxidization, polyamine compound may be immobilized by reacting amino groups thereof with the functional groups directly or via coupling agent or spacer to the surface of base material.

Detailed Description Text (21):

Though it is possible to immobilize polyamine compound by the above method, it is preferable in the present invention to immobilize polyamine compound by a method comprising a process to introduce surface graft radicals having reactive functional groups on the surface of base material and a process to immobilize the polyamine compound to these reactive functional groups. Surface graft radicals having reactive functional groups are a graft chain which has as the component a monomer having acid halogen radicals, isocyanate radicals and epoxy radicals, etc. in its molecule. Examples include (metha)acrylic halide such as (metha)acrylic chloride and (metha)acrylic bromide, (metha)acryloyloxyalkyl isocyanate such as 2-(metha)acryloyloxyethyl isocyanate, 3-(metha)acryloyloxypropyl isocyanate, 4-(metha)acryloyloxybutyl isocyanate, (metha)acryloyloxyisopropyl isocyanate, 2-(metha)acryloyloxy-1-ethylmethylethyl isocyanate, 2-(metha)acryloyloxy-1-ethylethylisocyanate, 4-(metha)acryloyloxy-2-ethylbutyl isocyanate, 2-(metha)acryloyloxy-2,2-dimethylethyl isocyanate, and a monomer containing epoxy groups such as 2,3-epoxypropyl (metha)acrylate, 3,4-epoxybutyl (metha)acrylate, 2,3-epoxyisobutyl (metha)acrylate, 3,4-epoxy-1-methylbutyl (metha)acrylate, 2,3-epoxy-1-methylethyl acrylate. In the present invention, graft chain composed by monomer having epoxy groups such as glycidyl acrylate or glycidyl methacrylate is preferable.

Detailed Description Text (24):

The form of the pathogenic substance selectively removing material of the present invention is not particularly restricted. For example, it may be in an arbitrary form of beads, hollow fiber, flat membrane, unwoven cloth, woven cloth or porous membrane comprising tube-like porous body, but preferably in the porous membrane form. Porous membrane herein means a membrane having through holes which allow filtration of a test sample. In the present invention, the membrane is preferably consisted of a base material prepared by forming a hydrophobic material such as polypropylene or polyvinylidene fluoride which has excellent dimensional stability and demonstrates low swelling against water into a membrane, and then by giving hydrophilic property to the membrane surface by surface treatment with coating of such hydrophilic polymer or graft polymerization.

Detailed Description Text (25):

When the form of the pathogenic substance selectively removing material of the present invention is porous membrane, the values related to the porous membrane such as pore size depend on the object to capture, membrane thickness, lamination of the membrane, i.e. number of layers laminated or the like. It is desirable to set these values within a range which does not allow clogging when the membrane is made into module and yet does not lower the removal rate. In the present invention, the material is preferably

in the form of porous membrane with the maximum pore size of 0.1-50.0 μm , void volume of 20-95%, water transmission rate of 10 ml/min/ m^2 /mmHg or more, or unwoven cloth in which a large number of filaments with the average diameter of 100 μm or less are crossed.

Detailed Description Text (26):

In the case of porous membrane, if the maximum pore size is less than 0.1 μm , fluid transmission speed becomes slow and the possibility of clogging is high. On the other hand, if the pore size exceeds 50.0 μm , the interaction with the object to be adsorbed becomes insufficient. If the void volume is less than 20%, sufficient transmission speed is not achieved, but if it exceeds 95%, a problem in the physical strength may arise. If the water transmission rate is less than 10 ml/min/ m^2 /mmHg, the transmission pressure tends to increase. To be more precise, it is preferable that the maximum pore diameter of the porous membrane is 0.1-5 μm for plasma and culture solution, and 5-50 μm if cells are contained in the sample. When the pathogenic substance selectively removing material of the present invention is provided in the form of porous membrane, the most preferable maximum pore diameter is 0.2-1.0 μm , void volume 40-90% and water transmission rate 100 ml/min/ m^2 /mmHg or more. The values shown herein are those obtained when said polyamine compound is immobilized on the base surface. It is preferable to immobilize polyamine compound not only on the outer surface of the membrane but also into the inner surface of pores.

Detailed Description Text (28):

For the material of the present invention to selectively remove pathogenic substances from a protein containing solution, it is preferable that the adsorbing property of the material surface is low. When the material is provided in the form of porous membrane, it is preferable that the surface is improved with flexible polymers having non-swelling property against water, i.e. having swelling rate of 20% or less, and the glass transition point of 290K or less to maintain sufficient transmission function without clogging the pores. Examples of such polymer include polymers and copolymers having monomers of alkoxyalkyl acrylate such as methoxyethyl acrylate as a major component.

Detailed Description Text (29):

For the removal of pathogenic substances by the material of the present invention, it is sufficient to have the material of the present invention bring into contact with the fluid containing pathogenic substances. To be more precise, this is carried out by batch system including immersion method, flow system making use of various forms of column and filtration system using a filter, but it is most preferable to apply filtration system using a filter. In addition to applying the material of the present invention by the above mentioned systems in known separation method and separation device using columns and membrane modules, it may also be used by itself as well as in combination by kneading, inner packing and lamination with other material to be made into health control products and pharmaceutical products for the purpose of prevention and diagnosis of virus infection or the like.

Detailed Description Text (30):

Though the pathogenic substance selectively removing material of the present invention may be used for various purposes, it is preferably employed for detection, separation, preservation and culture of viruses, bacteria and cells since it has affinity to and biological activity in many viruses, bacteria and cells. In particular, it is useful in selectively recognizing cells and viruses in an environment in which protein coexists.

Detailed Description Text (31):

In the present specifications, the word "virus" refers not only to a virus in complete form but also to its fragment. "Selective removal of virus" means not only physically removing virus but also inactivate or decrease the virus activity and lower or eliminate the virus infection. The capacity of virus removal is evaluated by measuring how much of the marker virus (10.^{sup.2} pfu/ml or more) added to the fluid before filtration is captured or removed not by the separation owing to size but by the interaction with the material surface. As a marker virus, herpes virus (HSV-1), ϕ X174 and AIDS virus (HIV) may be used. It is preferable that based on the above definition the pathogenic substance selectively removing material of the present invention demonstrates the virus removal rate of at least 90%, preferably 99% or more, against a plural types of viruses with different properties.

Detailed Description Text (32):

The pathogenic substance selectively removing material of the present invention may be used to remove virus from a fluid such as plasma, in which protein exists in mixture. It

is also preferably used in an environment with risk of virus infection through dispersion of and contact with blood and body fluid. Examples of such application include medical tools used in the medical institutions and first aid treatment in relation to, or daily commodities used by those infected with virus or likely to become infected, daily commodities used by healthy people for the purpose of preventing virus infection and back up use concurrently used with virus inactivation method making use of heat and drugs. Furthermore, it may also be used in a product such as air filter which provides virus-free environment.

Detailed Description Text (36):

The blood filter of the present invention is described in more detail by referring to the drawing. FIG. 1 shows the cross section of one embodiment of the blood filter of the present invention. The blood filter shown in FIG. 1 comprises a housing 4 which has a blood inlet 2 and a blood outlet 3 and a filter material 5 provided between supporting members 6a and 6b inside the housing 4. The filter material 5 is positioned so as to intercept the passage from the blood inlet 2 to the blood outlet 3 in the housing 4, and the peripheral portion of the filter material 5 or/and the supporting members 6a and 6b are closely joined with the inner wall of the housing 4 so as to make all the blood flowing into the housing 4 pass through the filter material 5. Porous membrane is used as the filter material 5, and the blood which flows from the blood inlet 2 to the housing 4 passes through the filter material 5 and then the blood outlet 3 to be discharged outside.

Detailed Description Text (39):

The polymer or copolymer of aziridine compound which is preferably used as a polyamine compound immobilized on the filter material surface of the blood filter of the present invention mainly has secondary or tertiary amino groups which are weak basic anion exchange groups in its molecule. For this reason, the electrostatic interaction with platelets becomes weak compared to that of polycationic compound having quaternary ammonium groups which are strong basic anion exchange groups in its molecule. By controlling the molecular weight, it is possible to easily control the interaction with platelets in the case of a polymer of aziridine compound. Due to this property, it is possible to obtain a surface which can capture platelets without activating them. In the blood filter of the present invention, polyethyleneimine among aziridine compounds is particularly preferable since it is inexpensive and easily obtainable. Its average molecular weight is preferably 500-8,000 and more preferably 600-3,000 for the purpose of providing a balance between the activation and adsorption of platelets on the filter material surface. The molecular weight and charge density of the polymer of aziridine compound immobilized on the filter material surface have considerable influence on the adsorption and activation of platelets. For example, when polyethyleneimine having a large molecular weight is immobilized on the surface, the charge as polycation becomes large, resulting in a tendency to activate platelets and damage cellular membrane. On the other hand, when polyethyleneimine having a small molecular weight is immobilized, the electric charge density becomes smaller and thus it is difficult to improve the platelet removal rate.

Detailed Description Text (43):

c. With reference to ASTM-F316, the maximum pore size of the membrane was obtained from the value measured by the bubble point method using isopropyl alcohol as a solvent. The maximum pore size is the value which indicates the maximum pore diameter of the pores which uniformly exist over the membrane after its formation, and does not include larger pores of pin holes and large holes having a larger diameter than the maximum pore diameter which are generated after membrane formation.

Detailed Description Text (45):

e. Plaque method was used for the assay of virus. To be more precise, the specimen was contacted with host cell or host bacterium, and the number of plaques generated by virus infection was obtained. The virus removal rate (virus capture rate) was calculated from the following formula (B) on the basis of this value.

Detailed Description Text (47):

A. Manufacture of polypropylene porous membrane

Detailed Description Text (48):

Per 100 parts by weight of the mixture of 2 types of polypropylenes (mixture weight ratio 100:40) having melt flow index of 30 and 0.3 respectively, 320 parts by weight of liquid paraffin (number-average molecular weight 324) and 0.3 part by weight of 1,3,2,4-bis(p-ethylbenzylidene) sorbitol as a crystal nucleus forming agent were melted and kneaded into pellets by a biaxial extruder. Using said extruder, these pellets were

melted at 150.degree.-200.degree. C. and extruded through a T die with the slit width of 0.6 mm. Cooling and setting solution comprising polyethylene glycol was arranged immediately under the T die. The melted product extruded into the air was led into the cooling and setting solution by rotating a guide roller provide in the solution, thereby cooling and setting the product, after which it was rolled off. The rolled film was cut into a prescribed length and immobilized in both the longitudinal and lateral directions, immersed in 1,1,2-trichloro-1,2,2-trifluoroethane for 10 minutes.times.4 times (total of 40 minutes), and the liquid paraffin was extracted. This was subsequently heat treated for 2 minutes in the air at 135.degree. C. to obtain a polypropylene porous membrane with the maximum pore diameter of 0.5 .mu.m, void ratio of 69% and membrane thickness of 80 .mu.m.

Detailed Description Text (49):

B. Surface treatment of the porous membrane for suppressing protein adsorption

Detailed Description Text (50):

Argon plasma (100 W, 0.1 Torr, 15 sec.) was irradiated to the polypropylene porous membrane thus obtained, which was then brought into contact with 2-methoxyethyl acrylate gas (1.0 Torr) for 3 minutes and then with glycidyl acrylate gas (0.7 Torr) for 1 minute to perform surface graft polymerization. As a result, hydrophilic porous membrane having reactive functional groups on the surface was obtained.

Detailed Description Text (52):

As the next step, this porous membrane was immersed for 18 hours at 60.degree. C. in an aqueous solution containing 1 wt. % spermidine and 0.5 wt. % pyridine as catalyst to immobilize spermidine on the membrane surface. The membrane obtained was washed thoroughly with methanol and used as the test sample. Spermidine bound to poly-(2-methoxyethyl acrylate) and glycidyl groups introduced into the surface of the polypropylene membrane was confirmed by IR (ATR method), NMR and ESCA. The membrane had the void volume of 65%, water transmission rate of 380 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.5 .mu.m.

Detailed Description Text (53):

D. Measurement of virus removal rate

Detailed Description Text (54):

This membrane was set in a Swin-Lock filter holder (manufactured by Nuclepore) (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.sup.4 PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99% in human plasma. When similar test was performed on .phi.X174 (bacteriophage), the removal rates of 99.9% or more in PBS buffer and 99% in human plasma were demonstrated.

Detailed Description Text (56):

Except for 1 wt. % spermine used instead of spermidine, the same procedure as shown in steps A through C in Example 1 was performed to obtain a porous membrane. This membrane had the void volume of 64%, water transmission rate of 380 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.5 .mu.m.

Detailed Description Text (57):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.sup.4 PFU/ml of hepes virus type I H.F strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 98% in human plasma were demonstrated.

Detailed Description Text (59):

A solution prepared by dissolving 18 parts by weight of polyvinylidene fluoride powder (manufactured by Mitsubishi Yuka, Kynar K 301) in 73.8 parts by weight of acetone and 8.2 parts by weight of dimethylformamide was cast over a polyethylene terephthalate film. This was immersed in a 1,1,2-trichlorotrifluoroethane solution for 5 minutes and then dried to obtain a polyvinylidene fluoride porous membrane having the membrane thickness of 125 .mu.m and the maximum pore diameter of 0.45 .mu.m.

Detailed Description Text (60):

This polyvinylidene fluoride porous membrane was treated in the same manner as

described in the step B of Example 1 for graft polymerization of 2-methoxyethyl acrylate to the membrane surface, and processed as shown in the step C of Example 1 to obtain a membrane in which spermidine was immobilized. This membrane had the void volume of 71%, water transmission rate of 430 ml/min/m.^{sup.2} /mmHg and the maximum pore diameter of 0.45 .mu.m.

Detailed Description Text (61):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 98% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 98% in human plasma were demonstrated.

Detailed Description Text (63):

Polypropylene unwoven cloth (manufactured by Tonen Co., Ltd., Tapirus) was treated by the steps B and C in Example 1 to obtain a membrane in which spermidine was immobilized.

Detailed Description Text (64):

Twenty pieces of this membrane were laminated and set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 99% in human plasma were demonstrated.

Detailed Description Text (66):

After irradiation of argon plasma (100 W, 0.1 Torr, 15 sec.), the polypropylene porous membrane obtained by the step A of Example 1 was brought into contact with glycidyl acrylate gas (0.7 Torr) for 5 minutes to perform surface graft polymerization. As a result, a hydrophilic porous membrane having reactive functional groups on the surface was obtained. Subsequently, this porous membrane was immersed for 5 hours at 60.degree. C. in an aqueous solution containing 1 wt. % spermidine and 0.5 wt. % pyridine to immobilize spermidine on the membrane surface.

Detailed Description Text (67):

Three pieces of this membrane were laminated and set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 91% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 90% in human plasma were demonstrated.

Detailed Description Text (69):

Surface graft polymerization of 2-methoxyethyl acrylate and glycidyl acrylate was performed on the membrane by the method described in the steps A and B of Example 1, and the virus removal rate was determined by the method described in the step D of Example 1 without immobilizing polyamine compound.

Detailed Description Text (70):

The removal rates of herpes virus and .phi.x174 in PBS buffer and human plasma were both 50% or lower.

Detailed Description Text (72):

After irradiation of argon plasma (100 W, 0.1 Torr, 15 sec.), the polypropylene porous membrane obtained from the step A in Example 1 was brought into contact with 2-methoxyethyl acrylate gas (0.8 Torr) for 3 minutes and 4-vinylpyridine gas (0.8 Torr) for 2 minutes for surface graft polymerization. By treating the membrane for production of quaternary ammonium in methanol containing 0.1 mol of benzylchloride at 55.degree. C. for 3 hours, a porous membrane having pyridinium structure on the surface was obtained. This membrane had the void volume of 63%, water transmission rate of 120 ml/min/m.^{sup.2} /mmHg and the maximum pore diameter of 0.5 .mu.m.

Detailed Description Text (73):

When the virus removal rate of this porous membrane was determined by the method used

in Example 1, the removal rate of 99% or more was demonstrated in PBS buffer against herpes virus and .phi.X174, but the removal rate of against both was 50% or lower in human plasma.

Detailed Description Text (75):

A. Manufacture of polypropylene porous membrane

Detailed Description Text (76):

The same procedure as described in the step A of Example 1 was performed to obtain a polypropylene porous membrane having the maximum pore diameter of 0.5 .mu.m, void volume of 58% and membrane thickness of 80 .mu.m.

Detailed Description Text (77):

B. Surface processing of porous membrane for suppressing protein adsorption

Detailed Description Text (78):

After irradiating argon plasma (100 W, 0.1 Torr, 15 sec.), surface graft polymerization was performed on the polypropylene filter thus obtained by bringing it into contact with 2-methoxyethyl acrylate gas (1.0 Torr) for 3 minutes and subsequently with glycidyl acrylate gas (0.7 Torr) for 3 minutes. As a result, hydrophilic porous membrane having reactive functional groups on the surface was obtained.

Detailed Description Text (80):

By immersing this porous membrane for 18 hours at 60.degree. C. in an aqueous solution containing 1 wt. % polyethyleneimine (molecular weight 1,800) and 1.0 wt. % pyridine, polyethyleneimine was immobilized on the membrane surface. The membrane obtained was thoroughly washed with water and methylene chloride/methanol azeotropic solvent.

Detailed Description Text (81):

Polyethyleneimine bound to glycidyl groups and poly(2-methoxyethyl acrylate) introduced to the surface of porous membrane were confirmed by IR (ATR method). The N/C ratio obtained by ESCA was 0.06. The amount of amine obtained by perchloric acid titration was 3.3.times.10.sup.-4 eq/g. This membrane had the void volume of 55%, water transmission rate of 390 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.52 .mu.m.

Detailed Description Text (82):

D. Measurement of virus removal rate

Detailed Description Text (83):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.sup.4 PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99.9% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 99.8% in human plasma were demonstrated.

Detailed Description Text (85):

Using polyvinylidene fluoride filter (manufactured by Millipore) as the porous membrane, and except for using glycidyl methacrylate instead of glycidyl acrylate and polyethyleneimine having the molecular weight of 70,000 instead of polyethyleneimine with the molecular weight of 1,800, the same procedure as described in steps B and C in Example 6 was performed. As a result, a polyvinylidene fluoride filter in which polyethyleneimine (molecular weight 70,000) was immobilized on the surface of filter was prepared. The N/C ratio of this membrane determined by ESCA was 0.08 and the amount of amine obtained by perchloric acid titration was 4.8.times.10.sup.-4 eq/g. This membrane had the void volume of 61%, water transmission rate of 380 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.50 .mu.m.

Detailed Description Text (86):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.sup.4 PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99.9% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 99.8% in human plasma were demonstrated.

Detailed Description Text (88):

After irradiating argon plasma (100 W, 0.2 Torr, 20 sec.), surface graft polymerization was performed on the polypropylene porous membrane obtained from the step A in Example 6 by bringing it into contact with glycidyl acrylate gas (0.7 Torr) for 3 minutes. As a result a hydrophilic porous membrane having reactive functional groups on the surface was obtained.

Detailed Description Text (89):

This porous membrane was immersed in an aqueous solution containing 1 wt. % polyethyleneimine (molecular weight 70,000) and 0.5 wt. % pyridine at 60.degree. C. for 18 hours to immobilize polyethyleneimine on the membrane surface. The membrane obtained was thoroughly washed with water and methylene chloride/methanol azeotropic solvent and used as the test sample. This membrane had the void volume of 57%, water transmission rate of 352 ml/min/m.^{sup.2} /mmHg and the maximum pore diameter of 0.49 .mu.m. The N/C ratio obtained by ESCA was 0.07 and the amount of amine obtained by perchloric acid titration was 4.4.times.10.^{sup.-4} eq/g.

Detailed Description Text (90):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 98.3% in human plasma. When similar test was performed on .phi.x174 and HIV, the removal rates of 99.9% or more in PBS buffer and 99.8% in human plasma against both were demonstrated.

Detailed Description Text (92):

Except that polyallylamine (molecular weight 10,000) as a polyamine compound was used instead of polyethyleneimine, the same procedure as described in the steps A through C of Example 6 was performed to obtain a polypropylene porous membrane in which polyaryllamine was immobilized on the surface. This membrane had the void volume of 56%, water transmission rate of 348 ml/min/m.^{sup.2} /mmHg and the maximum pore diameter of 0.49 .mu.m. The N/C ratio of this membrane obtained by ESCA was 0.05 and the amount of amine obtained by perchloric acid titration was 5.1.times.10.^{sup.-4} eq/g.

Detailed Description Text (93):

This membrane was set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of the plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99.6% in human plasma. When similar test was performed on .phi.X174 and HIV, the removal rates of 99.9% or more in PBS buffer and 99.8% in human plasma against both were demonstrated.

Detailed Description Text (95):

Except that the polypropylene unwoven cloth (manufactured by Tonen Co., Ltd., Tapirns) was used as a membrane and polyethyleneimine (molecular weight 1,200) as a polyamine compound was used, the same procedure as described in the steps B and C of Example 6 was performed and the membrane in which polyethyleneimine (molecular weight 1,200) was immobilized was obtained.

Detailed Description Text (96):

Thirty pieces of this membrane were laminated and set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 10 ml of PBS buffer (pH 7.35-7.6) containing about 10.^{sup.4} PFU/ml of herpes virus type I H.F. strain and 10 ml of the plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 98.3% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 99.7% in human plasma were demonstrated.

Detailed Description Text (98):

Except for using polyethyleneimine having molecular weight of 70,000 as a polyamine compound, the same procedure as described in the steps B and C of Example 6 was performed on a polyurethane porous filter (manufactured by Toyo Polymer Co., Ltd., Rubicell) and the membrane in which polyethyleneimine (molecular weight 70,000) was immobilized was obtained. This membrane had the void volume of 82%, water transmission rate of 1.1.times.10.^{sup.4} ml/min/m.^{sup.2} /mmHg and the maximum pore diameter of 18 .mu.m. The amount of amine obtained by perchloric acid titration was 1.6.times.10.^{sup.-4} eq/g.

Detailed Description Text (99):

Twenty pieces of this membrane were laminated and set in a Swin-Lock filter holder (.phi.25 mm), and using the membrane, 30 ml of PBS buffer (pH 7.35-7.6) containing about 10.sup.4 PFU/ml of herpes virus type I H.F. strain and 30 ml of plasma sampled from human fresh blood were filtrated to determine the virus removal rate of the membrane. The virus removal rate was 99.9% or more in PBS buffer and 99.1% in human plasma. When similar test was performed on .phi.X174, the removal rates of 99.9% or more in PBS buffer and 99.4% in human plasma were demonstrated.

Detailed Description Text (101):

The same procedure as described in the steps A and B in Example 6 was performed to obtain a polypropylene porous membrane having 2-methoxyethyl acrylate and glycidyl acrylate graft-polymerized on the surface of the membrane. This membrane had the void volume of 59%, water transmission rate of 434 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.5 .mu.m.

Detailed Description Text (102):

The virus removal rate of this membrane was measured by performing the same procedure as described in the step D in Example 6 but without immobilizing a polyamine compound on the membrane surface. The removal rates of herpes virus and .phi.X174 in PBS buffer and plasma were both 50% or lower.

Detailed Description Text (104):

Except that polyethyleneimine having an average molecular weight of 1,200 was used as a polyamine compound, and immobilization was performed at 60.degree. C. for 1 hour on the porous membrane obtained by the same procedure as described in steps A and B in Example 6, the same procedure as in the step C in Example 6 was performed, and the membrane in which polyethyleneimine was immobilized on the surface was prepared. This membrane had the void volume of 57%, water transmission rate of 365 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.50 .mu.m. The N/C ratio obtained by ESCA was 0.004 and the amount of amine obtained by perchloric acid titration was 0.7.times.10.sup.-4 eq/g.

Detailed Description Text (105):

By performing the same procedure as described in the step D in Example 6, the virus removal rate of this membrane was measured. The removal rates of herpes virus in PBS buffer and human plasma were respectively 99.9% and 50% or less. The respective removal rates of .phi.X174 were 99.9% and 50% or less.

Detailed Description Text (106):

As shown in the above, this membrane is highly capable of removing the virus in the water but does not demonstrate satisfactory function of removing virus from plasma.

Detailed Description Text (108):

After irradiating argon plasma (100 W, 0.1 Torr, 15 sec.), the polypropylene porous membrane obtained from step A in Example 6 was brought into contact with 2-methoxyethyl acrylate (0.8 Torr) for 3 minutes and then with 4-vinylpyridine (0.8 Torr) for 2 minutes for surface graft polymerization.

Detailed Description Text (109):

Then this membrane was treated in methanol containing 0.1 mol of benzyl chloride at 55.degree. C. for 3 hours, and as a result, a membrane having pyridinium structure on the surface was obtained. This membrane had the void volume of 57%, water transmission rate of 1.times.10.sup.4 ml/min/m.sup.2 /mmHg and the maximum pore diameter of 0.48 .mu.m.

Detailed Description Text (110):

When the virus removal rate of this membrane was measured by the same method as described in step D of Example 6, the removal rate of 99.9% against herpes virus and .phi.X174 was demonstrated in PBS buffer, but the rate went down to 50% or lower in human plasma.

Detailed Description Text (112):

A. Preparation of porous membrane

Detailed Description Text (113):

i) Porous membrane test sample 1

Detailed Description Text (114):

Soxhlet washing of polyurethane porous body having the maximum pore diameter of 18 μm and the void volume of 86% (manufactured by Toyo Polymer, Rubicell) was performed with methanol to remove impurities present in the membrane. The porous body was thoroughly dried, and then irradiated with low temperature plasma (ArO , 2 Torr) for 20 seconds, after which surface graft polymerization was done by supplying glycidyl methacrylate gas for reaction at the temperature of 288K for 5 minutes. This porous body was then immersed in an aqueous solution (containing 1 wt. % pyridine) of 1 wt. % polyethyleneimine (molecular weight 1,200) at 60.degree. C. for 18 hours. This was then washed well with ion-exchanged water and dried to be used as the test sample 1.

Detailed Description Text (115):

ii) Porous membrane test sample 2

Detailed Description Text (117):

iii) Preparation of porous membrane test sample 3

Detailed Description Text (119):

iv) Porous membrane test samples 4-8

Detailed Description Text (120):

Test samples 4-8 were prepared by immobilizing; respectively, Cationon UK (manufactured by Ippasha Yushi Industry), Panfix PX, or poly(1-ethylimino-2-guanydinoimidazole monohydrochloride) (manufactured by the same), polyethyleneimine (average molecular weight 300), polyethyleneimine (average molecular weight 10,000) or polyethyleneimine (average molecular weight 7,000) on a polyurethane porous body having the maximum pore diameter of 18 μm and void volume of 86% (manufactured by Toyo Polymer, Rubicell) according to the same method used for the test sample 1. Cationon UK immobilized on the test sample 4 and Panfix PX immobilized on the test sample 5 were as follows. ##STR8##
v) Porous membrane test sample 9

Detailed Description Text (121):

Surface graft polymerization was performed by irradiating polyurethane porous body having the maximum pore diameter of 18 μm and void volume of 86% (manufactured by Toyo Polymer, Rubicell) with low temperature plasma (ArO , 2 Torr) for 20 seconds, and then supplying it with vinyl pyridine gas for reaction at the temperature of 288K for 5 minutes. The porous body was then treated with 1% benzyl chloride in methanol solution at 55.degree. C. for 3 hours to produce quaternary amine. As a result, the test sample 9 having poly N-benzylvinylpyridinium chloride on the surface was obtained.

Detailed Description Paragraph Equation (2):

Virus removal rate (%) = $\{(1 - \text{number of surviving viruses}) / (\text{number of viruses in the stock solution})\} \times 100$ (B)

CLAIMS:

1. A material which removes viruses from a protein containing solution comprising a base material, a surface graft radical introduced onto a surface of said base material and a polyamine compound immobilized on a surface of the base material through the surface graft radical, wherein said polyamine compound is at least one type of compound selected from the group consisting of:

(a) a polyamine compound which has primary and secondary amines in its molecule and a hydrophobic part between these amines,

(b) a polyamine compound represented by the following formula (I): ##STR9## wherein $R_{\text{sup.1}}$, $R_{\text{sup.2}}$, $R_{\text{sup.3}}$, $R_{\text{sup.4}}$ and $R_{\text{sup.5}}$ independently represent substituents selected from the group consisting of hydrogen, aliphatic and aromatic hydrocarbons, and halogen, and n is 5 or more, and

(c) a polyamine compound represented by the following formula (II): ##STR10## wherein R represents $\text{NH}_{\text{sub.2}}$ or an aminoalkyl group having 1 to 4 carbon atoms and n is 5 or more.

2. The material according to claim 1, which is in the form of porous membrane.

3. A blood filter comprising a housing which has an inlet and outlet, and the material according to claim 1, which is arranged inside said housing and is in the form of porous membrane.

4. The blood filter according to claim 3, wherein the maximum pore diameter of said porous membrane ranges from 5-50 .mu.m.

5. A material which removes viruses from a protein containing solutions comprising a base material, a surface graft radical introduced onto a surface of said base material and a polyamine compound immobilized on a surface of the base material through the surface graft radical, wherein said polyamine compound is at least one type of compound selected from the group consisting of:

(a) a polyamine compound which has primary and secondary amines in its molecule and a hydrophobic part between these amines,

(b) a polyamine compound represented by the following formula (I); ##STR11## wherein R.sup.1, R.sup.2, R.sup.3, R.sup.4 and R.sup.5 independently represent substituents selected from the group consisting of hydrogen, aliphatic and aromatic hydrocarbons, and halogen, and n is 5 or more, and

(c) a polyamine compound represented by the following formula (II): ##STR12## wherein R represents NH.sub.2 or an aminoalkyl group having 1 to 4 carbon atoms and n is 5 or more, and wherein said surface graft radical is a graft chain composed of a monomer having at least one radical selected from the group consisting of an acid halogen, an isocyanate and an epoxy radical in its molecule as a reactive functional group.

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File: USPT

Aug 20, 1996

US-PAT-NO: 5547576

DOCUMENT-IDENTIFIER: US 5547576 A

TITLE: Pathogenic substance removing material and a blood filter containing the material

DATE-ISSUED: August 20, 1996

INVENTOR-INFORMATION:

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Shimura; Kenichi	Machida			JP

US-CL-CURRENT: 210/500.37; 210/435, 210/446, 210/490

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWC
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☐ 2. Document ID: US 4791063 A

L13: Entry 2 of 2

File: USPT

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DOCUMENT-IDENTIFIER: US 4791063 A

TITLE: Polyionene transformed modified polysaccharide supports

DATE-ISSUED: December 13, 1988

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US-CL-CURRENT: 435/243; 435/252.1, 435/308.1, 435/803, 524/27, 524/58, 525/54.3, 526/238.2

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWC
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